

deterioration of living conditions and of nutrition aggravating the prognosis of established disease. Or, thirdly, the deaths could be of persons who were being infected for the first time in greater numbers than normally because of increased exposure. No doubt in most countries there was a combination of all three factors.

In this respect the post-war fall, and in particular the rate of fall, is worth studying. Were the wartime rise due solely to the premature death of patients suffering from the disease we would expect a steep rise followed by a deeper fall, and it is possible that this may occur where conditions are severe enough to precipitate the death of patients with a bad prognosis, but not to provoke any great extension of the disease. This may partly explain the remarkable fall in France, but other factors must intervene also.* In nearly all other countries, where the pre-war decline was resumed at the same level or a higher level than would have been observed normally, it is obvious from the plotted rates for both world wars that there were many thousands of deaths from tuberculosis which would not have occurred but for the war. To what extent these were due in the main to aggravation of disease from which the patient normally would have recovered, and to what extent to new infections, must remain an open question.

We are far from a complete understanding of the nature of the wartime and post-war trends in tuberculosis. The uncertainty of our conclusions regarding widely differing trends, in for instance France, England, and Scotland, underlines the need for sounder and more detailed epidemiological study of tuberculosis in the future. Such study is at any time indispensable to a rational programme for eradication of the disease; it is particularly so at a time when our resources are limited, and action must be directed towards those groups of the community revealed in this way as being most susceptible to the disease. It will certainly be indispensable in the future when improvement in social services reaches the limit of reduction of tuberculosis by such means and we are left with the need for a real understanding of the disease if any further progress is to be made.

[The second lecture, with a list of references, will appear in our next issue.]

*One possible factor is the fall in consumption of alcohol since the introduction of rationing of wines and spirits in France during the war. This was followed by a marked fall in morbidity and mortality from diseases attributable to alcoholism, a fall not paralleled in any disease other than tuberculosis.

A residential college—the Midwife Teachers Training College—has been opened for midwives training for the Midwife Teachers Diploma awarded by the Central Midwives Board. The college is at High Coombe, Kingston Hill, Surrey, and will accommodate 16 students at a time for courses lasting six months. The first course is expected to begin in January, 1950. Intending candidates, who must satisfy the requirements laid down by the Rules (Section C) framed by the Central Midwives Board under the Midwives Acts, should apply for places to Mr. G. Thomas, Secretary, Midwife Teachers Training College Council, 72, Great Peter Street, London, S.W.1. Selected applicants will be required to give the council of the college a written undertaking that if they qualify they will serve as midwife teachers within the National Health Service for at least two years. The Minister of Health hopes that hospital boards and committees will encourage midwives likely to make good teachers to take advantage of these facilities. Suitable intending students should not be dissuaded from taking the course on the grounds that the hospital in which they are employed has no prospective vacancies for midwife teachers, since the scheme is intended to benefit the midwifery services as a whole.

RISK OF NEUROLOGICAL COMPLICATIONS IN PERNICIOUS ANAEMIA TREATED WITH FOLIC ACID

BY

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The identification and synthesis of pteroyl- γ -glutamic acid (folic acid*) by Angier *et al.* (1945, 1946) led to the early recognition of its quite unexpected and remarkable effects in the treatment of pernicious anaemia (Moore *et al.*, 1945) and of nutritional macrocytic anaemia (Spies *et al.*, 1945).

The results in pernicious anaemia were very striking at first, as many workers reported, including ourselves (Wilkinson, Israëls, and Fletcher, 1946). It soon became evident, however, that even when the blood counts were restored to normal levels relapses were occurring, and signs of involvement of the peripheral nerves, such as paraesthesiae and numbness in the limbs, and of the spinal cord tracts, like ataxia and loss of vibration sense, might not be improved or might become worse.

Even more important, however, was the fact that some patients who had not previously shown signs of nervous system disturbances developed such signs, often very acutely, after being treated with folic acid for variable periods. Since 1946 several groups of workers have become aware of this disquieting fact, and in consequence the widespread enthusiasm for folic acid, at least for the treatment of pernicious anaemia, has been rapidly waning.

TABLE I.—Summary of Cases Reported as Developing Neurological Changes

Authors	No. of Patients Treated	No. Developing Neurological Symptoms and Signs	Neurological Symptoms Made Worse
Schwartz, Armstrong (1947) ..	69	4	—
Heinle, Welch (1947) ..	47	3	—
Heinle <i>et al.</i> (1947)
Spies <i>et al.</i> (1948)
Spies, Stone (1947) ..	38	28	7 (out of 19)
Vilter, Vilter, Spies (1947)
Vilter, Vilter, Hawkins (1947)
Ross, Belding, Paegel (1948) ..	22	9	4
Israëls, Wilkinson (1949) ..	20	13	3
Wilkinson (1948, 1949)
Keil (1947) ..	19	1	—
Davidson, Girdwood (1947) ..	16	1	—
Hall, Watkins (1947) ..	14	"A significant proportion"	—
Hall, Watkins, Hargraves (1946)
Wagley (1948) ..	10	8	—
Castle, Berk (quoted Wagley, 1948) ..	10	1	—
Bethell, Sturgis (1948) ..	6	1	—
Bethell <i>et al.</i> (1946)
Jacobson <i>et al.</i> (1948) ..	—	2	—

In Table I we have included all the available references to the development of subacute combined degeneration of the spinal cord in patients with pernicious anaemia, or the worsening of neurological symptoms already present, after treatment with pteroyl- γ -glutamic acid.

From a careful study of the various reports it was obvious that many of them referred to the same groups of cases, since some authors have published their results and cases in several journals, often without cross-references, and in some reports no details are given at all, other than

*In this paper folic acid is used synonymously with and refers to the synthetic pteroyl- γ -glutamic acid.

the bare statement relating to the occurrence of neurological complications in a group of patients. We have therefore inserted in the table the latest figures of each group of workers, omitting their earlier ones in other papers.

These reports suggest that, though folic acid treatment for patients with pernicious anaemia will lead in most cases to a satisfactory remission of the anaemia temporarily, there is a risk that damage to the spinal-cord tracts may continue and may show itself even after the blood counts have been restored to normal (Wilkinson, 1948, 1949). It is quite clear that pteroyl- γ -glutamic acid will not control disease of the central nervous system already present when treatment is begun. Previous estimates of the risk of the development of nervous system disturbance have varied in the larger groups from three out of 47 (Heinle and Welch, 1947; Heinle *et al.*, 1947) to 28 out of 38 (Spies *et al.*, 1948). Except for the later groups few of these patients have been observed for more than 12 months; most of them were under control for shorter periods. The pernicious-anaemia-posterolateral-sclerosis syndrome is notoriously slow to develop, so in order to obtain a better estimate of the risk involved in the use of synthetic pteroylglutamic acid we have since early in 1946 been observing closely a group of 20 pernicious-anaemia patients, either in relapse or having had no previous treatment, only three of whom had initial evidence of subacute combined degeneration of the spinal cord. We treated these patients with pteroyl- γ -glutamic acid alone until signs and symptoms of central nervous system disease appeared, or until there were signs of exacerbation of the disease initially present, and we have observed them all at frequent intervals: our intermediate results have been reported elsewhere (Wilkinson, Israëls, and Fletcher, 1946; Wilkinson, 1948, 1949). Our results after three years' observation of the group show that at the time of writing (May, 1949) only four of these patients are still well on folic acid treatment.

Illustrative Cases

The patients are divided into four groups: (1) Four patients with signs of disease of the nervous system developing acutely during treatment; (2) nine patients with signs of disease of the nervous system developing gradually during treatment; (3) three patients who had disease of the nervous system initially; and (4) four patients who had not developed signs of disease of the nervous system at the time of writing.

Details of groups 1, 2, and 3 are given in Table II, and of group 4 in Table III. Illustrative case records of

patients in groups 1, 2, and 3 are given below. The patients in group 4 had the usual features of pernicious anaemia without neurological disturbance.

TABLE III.—Group 4 Cases (No Signs of Disease of Nervous System)

Case No.	Age	Sex	Initial Count		Period of Treatment (Months)	Final Count		Continuing Dose Folic Acid (mg. daily)
			R.B.C. 10 ⁶ /c.mm.	Hb g./100 ml.		R.B.C. 10 ⁶ /c.mm.	Hb g./100 ml.	
17	76	M	1.42	5.0	25	4.96	14.8	10
18	71	F	2.08	5.5	27	4.70	14.6	2.5
19	67	F	1.54	4.4	29	4.00	11.3	10
20	47	M	1.47	5.0	37	4.98	14.8	10

Group 1: Case 1

A married woman aged 63 was seen for the first time in May, 1946, complaining of dyspnoea, loss of weight, and increasing fatigue. She was pale and jaundiced, there was no enlargement of liver or spleen, and little abnormal was found in the heart and lungs. The arm and leg reflexes were normally active, plantar responses were flexor, and there were no subjective or objective sensory changes. A blood count showed: red cells, 1,640,000 per c.mm.; haemoglobin, 5.2 g. per 100 ml. The bone marrow was typically megaloblastic. There was complete achlorhydria gastrica.

She was admitted to hospital and given synthetic pteroyl- γ -glutamic acid, 20 mg. daily, by mouth. Her clinical condition and the anaemia improved steadily. After four weeks her red cells numbered 3,460,000 per c.mm. and the haemoglobin was 10.7 g. per 100 ml. Folic acid was reduced to 10 mg. daily, and after five months' treatment, when the haemoglobin was 14.2 g. per 100 ml., it was reduced to 2.5 mg. daily. This seemed to be too little, because after nine months the haemoglobin had fallen to 13.4 g. per 100 ml. and the red cells to 4,200,000 per c.mm. It was after nine months that she complained that her legs felt "as if she had wet stockings on," and examination showed that vibration sense was absent. The dose of folic acid was raised to 5 mg. daily. The nervous symptoms remained stationary until the 15th month, when within seven days she lost the use of her legs and became unable to walk. The blood count was then: red cells, 4,070,000 per c.mm.; haemoglobin, 11.8 g. per 100 ml.

Examination showed exaggerated reflexes, extensor plantar responses, absent vibration sense, and much-impaired position sense.

Folic acid treatment was immediately discontinued, and she was given liver extract intramuscularly and 30 g. of desiccated stomach daily by mouth. After one month her walking was improved, but the right plantar response was still extensor; after two months she was ambulant again and both plantar responses were flexor; after eight months all symptoms had disappeared and she has remained well since.

TABLE II.—Cases in Groups 1, 2, and 3. Patients Developing Neurological Changes on Folic Acid Treatment

Case No.	Age	Sex	Initial Count		Initial Neurolog. Signs	Period of Treatment (Months)	Final Hb Level g./100 ml.	Increasing Anaemia Present	Final Dose of Folic Acid mg. Daily	Signs of Disease of Nervous System							Recovery on Liver or Stomach (Months)
			R.B.C. 10 ⁶ /c.mm.	Hb g./100 ml.						Plantar Response	Knee-jerks	Ankle-jerks	Romberg's Sign	Paraesthesia Numbness	Vibration Sense	Joint Sense	
1	63	F	1.64	5.2	None	15	11.8	Yes	5	Extensor Flexor	+++	+++	+++	+++	Absent	Impaired	2
2	63	F	1.15	3.6	None	18	14.6	No	5	"	Dim.	—	+++	++	"	Absent	3
3	50	F	0.95	3.3	None	22½	10.5	Yes	30	"	Dim.	—	+++	++	"	Impaired	3
4	73	M	2.20	7.4	None	3	10.5	No	20	Doubtful	+++	+++	—	+++	"	Absent	—
5	51	F	1.82	5.8	None	12	11.8	Yes	20	Flexor	+	++	—	++	"	"	3
6	55	M	2.15	7.7	None	13	12.5	Yes	10	"	Dim.	++	—	+++	"	Impaired	3
7	45	M	1.53	5.0	a	5	11.8	Yes	15	"	+	+	—	+++	+	Present	3
8	56	F	2.06	7.2	None	6	13.8	No	20	"	+	+	+	+++	"	"	6
9	58	M	1.21	3.9	None	23	8.8	Yes	10	"	++	++	+	+++	Absent	Impaired	2
10	48	M	1.80	6.6	b	3	13.0	No	20	"	++	++	+++	+++	"	"	2
11	64	F	2.00	8.3	None	19	13.3	No	40	"	Dim.	Dim.	—	+++	"	"	—
12	56	F	1.31	5.2	Paraesth.	2	8.6	No	20	Extensor Flexor	++	—	—	+++	"	Impaired	3
13	31	F	1.31	4.8	None	35	14.4	No	10	"	++	++	++	++	"	"	—
14	53	M	2.92	7.2	c	2½	14.6	No	20	"	++	++	+	+++	"	Absent	1
15	46	M	3.83	13.3	d	1	13.3	No	20	"	++	++	—	+++	"	Present	1
16	70	F	2.13	8.8	Paraesth.	6	13.8	No	20	"	+	—	—	+++	"	Impaired	3

a = Stiffness and deformity of right arm present for 29 years, due to extrapyramidal lesion. b = Joint sense absent. c = Numbness of legs, absent vibration sense. d = Numbness and stiffness of fingers. Note: All patients had megaloblastic marrows initially and achlorhydria.

Group 2: Case 9

A joiner aged 58 was diagnosed as having pernicious anaemia some years before, but he had neglected treatment and when first seen his red cells had fallen to 1,210,000 per c.mm. and his haemoglobin to 3.9 g. per 100 ml. He was very pale and dyspnoeic, and had oedema of the feet and scrotum. The heart was not enlarged, but there was a generalized systolic murmur and occasional extrasystoles. His liver and spleen were slightly enlarged. In the central nervous system reflexes were normally active and plantar responses flexor; in spite of the oedema, sensation in the legs was normally appreciated. The bone marrow was megaloblastic, and achlorhydria was confirmed. He was given folic acid parenterally—at first 150 mg. intravenously, followed by 15 mg. intramuscularly on alternate days for 10 days; he was then given 20 mg. daily by mouth. He made a good recovery, and after two months, when his red cells numbered 4,200,000 per c.mm. and the haemoglobin was 11.6 g. per 100 ml., the folic acid was reduced to 10 mg. daily. After 4½ months' treatment the haemoglobin was 12.7 g. per 100 ml., and the dose was reduced to 5 mg. daily, and at nine months it was further reduced to 1.75 mg. daily, when his red cells numbered 5,060,000 per c.mm. and the haemoglobin was 13.8 g. per 100 ml. This latter dose was too small for maintenance: at 12 months the haemoglobin was only 13 g. per 100 ml., so the dose was raised to 2.5 mg. daily, and one month later to 10 mg. daily, when his red cells numbered 3,880,000 per c.mm. and the haemoglobin was 11.3 g. per 100 ml. At 14 months the red cells numbered 5,020,000 per c.mm. and the haemoglobin was 14.2 g. per 100 ml.; however, the first sign of disease of the nervous system appeared at this time—the patient complained of aching legs, but examination of the central nervous system revealed no objective abnormality.

The patient kept reasonably well until the 23rd month, when the blood count relapsed (red cells 2,930,000 per c.mm. and haemoglobin 8.8 g. per 100 ml.) and he had numbness and paraesthesiae in the arms and legs, and felt as if he were walking on cotton-wool.

Examination showed that his reflexes were still brisk and his plantar responses flexor, but vibration sense was now absent up to the knees and joint sense was impaired; Romberg's sign was present. He was given 30 g. of desiccated stomach daily, and he improved rapidly. Two months later his red cells were 4,920,000 per c.mm. and the haemoglobin was 13 g. per 100 ml. The only remaining neurological symptoms were slight paraesthesiae in the fingers.

Group 3: Case 15

A male cotton-spinner aged 46 had noticed that for the past five months his hands and fingers were becoming increasingly numb so that he could no longer handle the cotton threads; he also had some stiffness of the legs. He was not pale, and was well nourished; all tendon reflexes were brisk and equal on the two sides; the left plantar response was flexor, but the right was doubtful; cranial nerves were normal; vibration and joint sense were definitely present and normal. Other systems were normal. The blood count showed: red cells, 3,830,000 per c.mm.; haemoglobin, 13.3 g. per 100 ml. There was a definite megaloblastic marrow and an achlorhydria. The cerebrospinal fluid was not under pressure, proteins were 45 mg. per 100 ml., and there was slight globulin opalescence.

He was given folic acid, 20 mg. daily, but the blood count did not improve; after four weeks the red cells numbered 3,880,000 per c.mm. and the haemoglobin was still 13.3 g. per 100 ml.

Five weeks after starting folic acid treatment he complained that the numbness and paraesthesiae in the hands were much worse. Examination showed that vibration sense had now disappeared, but the reflexes were as before. Treatment with folic acid was therefore replaced with 30 g. of desiccated stomach. After one month of this he was much better, and his red cells numbered 4,740,000 per c.mm. and the haemoglobin was 14.2 g. per 100 ml. Ten months later he was back at work, but it was 16 months before all paraesthesiae had ceased and vibration sense had returned.

Discussion

We are not concerned here with the haematological and clinical effects of folic acid, which have been fully discussed elsewhere (Wilkinson, 1948, 1949), but only with its influence on the development of peripheral neuritis and subacute combined degeneration of the spinal cord in pernicious anaemia.

The accompanying Chart gives a graphic representation of the length of time during which treatment with pteroyl- γ -glutamic acid (folic acid) was given before the appearance

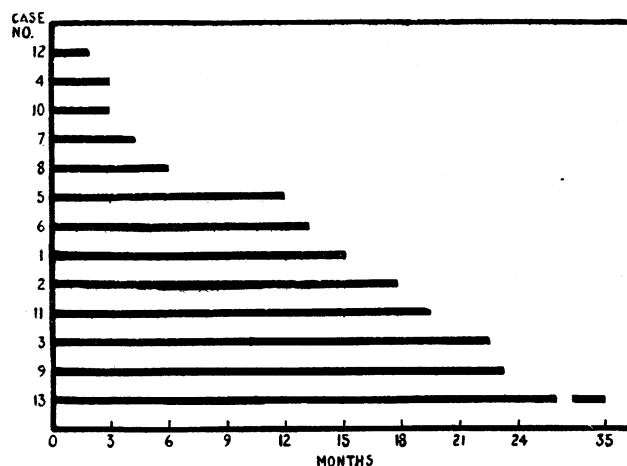


Chart showing the period that folic acid (pteroyl- γ -glutamic acid) treatment was given before the appearance of neurological signs made a change necessary.

of symptoms of subacute combined degeneration of the spinal cord. It is seen that the time of onset of neurological signs and symptoms of central nervous system disease is spread over a three-year period; apparently there is no time of special danger, nor is there any time after which the patient can be considered safe.

The relevant information about these patients in Table II shows, disappointingly, that none of these observations make it possible to predict the likely onset of neurological complications. Of the four patients in group 1 the periods of treatment varied from 3 to 22½ months. Of the 13 patients in groups 1 and 2 six showed a falling haemoglobin level, and seven did not, while the haemoglobin levels varied from 8.8 to 14.6 g. per 100 ml.

The results therefore show that in a three-year period 80% of the patients who were being treated with folic acid had developed or had increased signs and symptoms of nervous system disease that could be quite quickly controlled in the early stages by treatment with intramuscular liver extracts or oral desiccated stomach preparations. Thus there is obviously serious risk that patients with pernicious anaemia treated solely with folic acid may develop signs of disturbance of the central nervous system, or that any initial cord involvement or peripheral neuritis may get worse.

Nevertheless, four patients have been well maintained on folic acid alone for up to three years without any apparent disadvantage. Is there, therefore, any place for folic acid in the treatment of pernicious anaemia? The facts reported here and by others emphasize in a new way the dissociation between the haematological and neurological parts of the pernicious anaemia syndrome. It is well known that the neurological syndrome can occur in the absence of anaemia. We can now see that a minority (20%) of patients with pernicious anaemia do not develop (at least after three years) disease of the nervous system when an agent (folic

acid) that corrects only the haematological disorder is used for treatment. But there seems to be no way of picking out this fortunate minority; certainly, initial absence of signs of nervous disease is no help. Consequently, it is our considered opinion that folic acid ordinarily should not be used in the treatment of pernicious anaemia, and never in subacute combined degeneration of the spinal cord. Very rarely it may be of temporary use in the treatment of a pernicious-anaemia patient who cannot take stomach preparations and is hypersensitive to parenteral liver extracts, until the patient has been desensitized, although oral liver extracts will usually get over this problem.

While the acute neurological syndrome described here and by others is rarely seen in the natural course of postero-lateral sclerosis with pernicious anaemia, nevertheless its apparent direct association with folic acid therapy raises the possibility of a folic-acid/anti-folic-acid mechanism in the maintenance of the integrity of the central nervous system; but we have as yet no definite evidence that folic acid causes organic lesions in the cord. At any rate, the action of folic acid on the neurological system is not the same as that of the liver principle, although its initial effect on the bone marrow and blood appears to be very similar. We have also yet to see a patient with pernicious anaemia who would not respond to haemopoietically active liver extracts but would respond to folic acid; it turns out that such patients always have some other disease, such as idiopathic steatorrhoea.

Therefore, whatever the circumstances, folic acid, if used at all, should be replaced by liver or stomach as soon as possible, and those patients having folic acid should be seen at frequent and regular intervals so that the onset of neurological complications can be corrected without delay.

It has been our view that, while folic acid must not be used in the treatment of the pernicious anaemia syndrome on account of the risk of producing postero-lateral sclerosis in patients otherwise free from neurological symptoms, its use was allowable in the treatment of other megaloblastic anaemias that do not develop cord lesions, like those occurring in sprue, steatorrhoea, and pregnancy. This must now be reconsidered carefully in view of the recent observation by Meyer (1948) that combined system disease occurred in a patient with macrocytic anaemia secondary to ulcerative colitis of long standing. After treatment with folic acid for 18 months he quite quickly developed ataxia, loss of vibration and position sense in the legs, and positive pyramidal signs. These neurological complications appeared when the patient's haemoglobin level was normal and his weight satisfactory. Davidson and Girdwood (1948) have also reported the onset of neurological signs in two patients with idiopathic steatorrhoea who were having folic acid treatment; the signs in these patients could have been due to peripheral neuritis, and no pyramidal lesion was detected. It is only reasonable to point out that this neurological complication of non-Addisonian types of anaemia is extremely rare.

Summary

A group of 20 patients with pernicious anaemia, either untreated cases or relapsed cases, have been treated with synthetic pteroyl- γ -glutamic acid (folic acid) alone; three had initial signs of subacute combined degeneration of the spinal cord.

In a three-year period 13 patients without initial neurological involvement developed signs and symptoms of subacute combined degeneration of the spinal cord which were relieved by changing the treatment to liver extracts or desiccated stomach preparations.

Three patients with initial neurological symptoms and signs became worse neurologically after folic acid therapy.

There was no specially dangerous point during folic acid treatment, for the times at which nervous-system complications became serious were evenly distributed over three years.

Neither the presence or absence of increasing anaemia nor the haemoglobin levels could be used to predict the likelihood of neurological complications.

Four patients are quite well after two to three years on doses of 5–20 mg. of folic acid daily, given orally.

The use of folic acid for the treatment of pernicious anaemia should be strictly limited to the rare cases of special difficulty.

Folic acid should never be given to patients with subacute combined degeneration of the spinal cord.

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Delivering the chairman's address at the meeting of the Dental Board on May 11, Dr. Fish said that for the past year there had been a record decline in the total number of names on the *Dentists Register*. The figure was below that reached in 1939. About 90% of the dentists in active general practice in England and Wales, and a higher percentage of those in Scotland, were working in the National Health Service. When faced with more patients than he could comfortably treat, a dentist must do one of three things—add to his hours of work, refuse to see some patients, or speed up his work. He might even do all three. Probably most were now working longer hours than those recommended by the Spens Committee. Whether that added to their efficiency or to their enjoyment of life must remain an open question. Most dentists were in the dilemma that they must either refuse patients in need or hurry through the treatment of each in an effort to extend their services to all. The question was not whether they would condescend to work the Service but whether as individuals and as a profession they had the capacity for self-discipline, the ethical training, and the philosophy to rise to those heights of altruism which the Service demanded of them. For many there was no possibility of choice. The Service was their only means of livelihood. The success of the Service and the future of dentistry depended upon their willingness and capacity to sacrifice what might be legitimate personal gain for the salvation of their self-respect and the honour of their calling. Referring to the formation of dental companies under the influence of laymen, he said he did not think that any member of the profession should accept service under such conditions without the most careful consideration of what they implied.